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(12) # EUROPEAN PATENT APPLICATION

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(54) **Mono(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate, its preparation and pharmaceutical compositions containing it.**

(57) Mono (2-ammonium-2-hydroxymethyl-1,3-propanediol) (2R-cis)-(3-methyloxiranyl) phosphonate endowed with therapeutic activity as broad-spectrum antibiotic, as well as a method for preparing same from bis(2-ammonium-2-hydroxymethyl-1,3-propanediol)2R-cis)- (3-methyl-oxiranyl)phosphonate and a sulphonic acid.

Pharmaceutical compositions containing the novel mono(2-ammonium-2-hydroxymethyl- 1,3-propanediol)-(2R-cis)-(3-methyloxiranyl)phosphonate are also disclosed.

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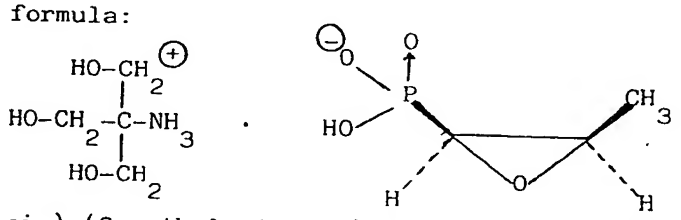
The present invention relates to a new soluble salt of (2R-cis)-(3-methyloxiranyl)phosphonic acid, the preparation thereof as well as the pharmaceutical compositions containing it.

The new salt of the invention, is the mono(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate of the formula:



(2R-cis)-(3-methyloxiranyl)phosphonic acid is also known as fosfomycin (Merck Index - 9th Edition - 4110).

Fosfomycin and the salts thereof with non-toxic bases are widely used in human and veterinary fields to inhibit the grouth of gram-positive and gram-negative pathogenous bacteria.

In the Italian Patent Application 25,853 A/78 filed on July 19, 1978 there was disclosed and claimed the bis(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate showing a tolerability and bioavailability remarkably more favourable than those of the sodium and calcium salts of fosfomycin.

However bis(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate gives very viscous solutions thus rendering difficult the administration of the salt by injectable route.

The Applicant has now found that mono(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate of the invention, while maintaining the advantages of bis(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate unchanged, has the further advantage to give solutions less

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viscous than those which can be obtained, the content of conventional fosfomycin being equal, when using bis(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate.

More particularly, a solution consisting of 688 mg and 1377 mg respectively of bis(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranym)phosphonate (corresponding to 250 mg and 500 mg respectively of conventional fosfomycin) in 2.5 ml of water solvent, shows a viscosity of 4.8 and 7.2 cps respectively, at 25 °C. The corresponding solutions obtained by dissolving 470 mg and 940 mg respectively of mono(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate in 2.5 ml of water solvent show at 25 °C a viscosity of 3.9 and 5.0 cps respectively.

Typical pharmaceutical preparations are:

(a) Administration by oral route (sachets)

The compositions for the oral route administration corresponding to 250 mg, 500 mg and 2000 mg of conventional fosfomycin contain (the amounts are in milligrams):

Mono(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate	470	940	3760
sodium carboxymethylcellulose	80	100	120
lactose	50	100	300
titanium dioxide	50	70	100
orange flavour	50	50	80
saccharose	2300	2740	5640

(b) Administration by parenteral route

For the administration by parenteral route a vial and an

ampoule of water for injectable preparation is used as solvent.

Each vial contains 470, 940 or 1880 mg respectively of the salt of the invention, in form of sterile powder.

At the time of administration, the sterile powder is dissolved in the solvent.

The amounts of solvent are 2.5 ml for each vial containing 470 mg and 940 mg of the salt of the invention and 5.0 ml for each vial containing 1880 mg of the compound of the invention.

The mono(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate of the present invention is prepared by reacting the bis(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate, prepared according to Italian Patent Application 25,853 A/78, with a sulphonic acid, such as for instance an alkylsulphonic, aralkylsulphonic, arylsulphonic acid. The preparation of the salt of the invention and the physico-chemical characteristics of the obtained product, are illustrated in the following example, which is however in any way limitative.

Example

A solution, previously heated at 75 °C, of 262.5 g (1.38 mol) of monohydrated 4-toluensulphonic acid in 1300 ml of absolute ethyl alcohol was added to a suspension of 500 mg (1.315 mol) of bis(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate in 3300 ml of absolute ethyl alcohol, heated under stirring at 70-75 °C.

At first the reagents go almost completely on solution and thereafter a colorless crystalline solid beginns to slowly precipitate. The suspension is slowly cooled under stirring to +3 °C, by means of a water-ice bath.

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The precipitate is then collected by filtration under vacuum and washed on the filter with 700 ml of absolute ethyl alcohol cooled to +10 °C.

After drying under vacuum at 40 °C for 16 hours, 291.3 g of the acid salt are obtained in form of a colorless microcrystalline powder which melts at 116 °C.

A sample for analysis is recrystallized by dissolution in warm methanol (ratio 1:2 p/v) and by addition of 4 volums of absolute ethyl alcohol to the thus obtained solution maintained under stirring and cooled to +3 °C.

^{1}H-NMR (D_2O) : (ppm) = 1.53 (d, 3H, CH_3)
3.50-2.75 (m, 2H, CH)
3.75 (s, 6H, CH_2)

$[\alpha]_{365}^{-20}$ (5% water) -12.5 °C

IR (in KBr) : 800 e 900 cm^{-1}

Claims

1. Mono(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3--methyloxiranyl)phosphonate.

2. Process for the preparation of mono(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phoshonate characterized in that the bis(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate is reacted with a sulphonic acid selected from the group comprising alkylsulphonic, arylsulphonic and aralkylsulphonic acids.

3. Pharmaceutical compositions comprising mono(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R-cis)-(3-methyloxiranyl)phosphonate together with pharmaceutically acceptable carriers.

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EUROPEAN SEARCH REPORT

Application number

EP 80 10 6108

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
D	THE MERCK INDEX, 9th Edition, 1976 ref.no. 4110, page 547: "Fosfomycin" Rahway, New York US * Whole article * --	1,3
	GB - A - 1 223 923 (MERCK) * Complete specification * --	1,3
PD	GB - A - 2 025 975 (ZAMBON) * Complete specification * ----	1,3

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 F 9/38
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TECHNICAL FIELDS SEARCHED (Int. Cl.³)

C 07 F 9/38

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	20-01-1981	BESLIER

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